Induction of pluripotency in fibroblasts by fusion with enucleated human embryonic stem cell syncytia

Grant Award Details

Induction of pluripotency in fibroblasts by fusion with enucleated human embryonic stem cell syncytia

Grant Type: SEED Grant

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Investigator:

Name:	Holger Willenbring
Institution:	University of California, San Francisco
Type:	PI

Human Stem Cell Use: Other

Cell Line Generation: Other

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Progress Reports

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View Report

Grant Application Details

Application Title: Induction of pluripotency in fibroblasts by fusion with enucleated human embryonic stem cell syncytia

Public Abstract:

Embryonic stem cells are pluripotent which means they can in principle be instructed to become every cell type in the body. Moreover, they can produce an infinite number of daughter cells. Therefore, human embryonic stem cells have great potential as a cell source for regenerative therapies of a wide range of diseases, some of which require the replacement of hundreds of millions of cells. A major obstacle towards the realization of regenerative therapies using for example neurons or liver cells derived from human embryonic stem cells is the immune reaction they provoke after transplantation. This is caused by markers all differentiated cells display on their surface which enable the body's immune system to distinguish potentially harmful foreign structures from its own cells. These so called histocompatibility markers are encoded in the genome and differ significantly between most humans which necessitates suppression of the immune system before incompletely matched cells or organs can be transplanted. Drugs effective at long-term immune suppression can cause severe side effects. Therefore, the creation of pluripotent stem cells that are matched to the recipient's histocompatibility complex would be desirable. Replacing an oocyte's nucleus with a nucleus from a fibroblast has been shown to lead to reprogramming and acquisition of pluripotency by the somatic cell's nucleus. This so called somatic cell nuclear transfer has highlighted an opportunity for the creation of pluripotent stem cells that would be perfectly matched for transplantation since they contain only the recipient's genome. However, both ethical and technical obstacles have hampered the development of this technology. In particular, the need for large numbers of oocytes has restricted this research to only a few laboratories in the world. Recently, a process called cell fusion has been found to enable the use of human embryonic stem cells for reprogramming of somatic cells. Cell fusion describes the melding of two or more cells which produces a single cell encompassed by the parental cells' membranes and containing their nuclei and cytoplasms. To render these fusion products useful for transplantation, the genome of the human embryonic stem cells would have to be eliminated. This can be achieved by centrifugation but appears to impede the reprogramming potential of embryonic stem cells. In contrast, oocytes retain reprogramming activity after enucleation which is attributed to the accumulation of nuclear factors in their large cytoplasm. The cytoplasm of human embryonic stem cells is small which we will compensate for by creating large embryonic stem cell fusion products. Based on our experience with mouse embryonic stem cells, these fusion products will retain pluri-potency and will undergo nuclear fusion. The resulting single, large nucleus can be completely removed and the increased availability of nuclear factors is expected to afford high reprogramming potential.

Statement of Benefit to California:

Pluripotent stem cells compatible with a patient's immune system would have great potential for therapy of a wide range of diseases. Somatic cell nuclear transfer into enucleated oocytes affords such an opportunity by reprogramming the somatic cell's nucleus to a pluripotent state. However, human oocytes are not readily available and this technology is both technically and financially demanding. Therefore, an available and affordable source of pluripotent stem cells for regenerative therapies would be highly desirable. This is particularly important as life expectancy especially in California is rising leading to increased incidences of diseases associated with aging. To decrease the costs of regenerative therapies and thus render them eventually available for every Californian citizen in need, alternative strategies aimed at generating patient-matched stem cells have to be developed. The method we propose to use for the induction of pluripotency in fibroblasts utilizes the reprogramming activity of human embryonic stem cells which have the capability to divide indefinitely and are therefore both readily available and affordable. Moreover, our cell fusion strategy is designed to limit the extent of manipulation of both the embryonic stem cell and the fibroblast which would eventually be derived from the patient. Thus, this approach is not technically challenging which further increases its efficiency and practicality. Consequently, we believe that reprogramming by cell fusion with enucleated human embryonic stem cells has potential as a method to produce pluripotent stem cells from fibroblast in a fashion that would be both effective and applicable in the clinic.